PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 95.83095/01	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/002925	International filing date *(day/month/year)* 07.07.2004	Priority date *(day/month/year)* 07.07.2003
International Patent Classification (IPC) or national classification and IPC A61K9/107, A61K47/44, A61K47/14		
Applicant NARES AB et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.05.2005	23.06.2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002925

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-22	as originally filed
Claims, Numbers	
1-18	received on 04.05.2005 with letter of 29.04.2005
Drawings, Sheets	
1/3-3/3	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002925

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13-18 regarding industrial applicability

because:

☒ the said international application, or the said claims Nos. 13-18 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002925

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1
	No:	Claims	2-18
Inventive step (IS)	Yes:	Claims	1
	No:	Claims	2-18
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I
Basis of the report

1) Amendments

Novel set of claims 1-18 is allowable according to Article 34(2)(b) PCT because a support was found in the description and the amendments introduce no subject-matter which extends beyond the content of the application as filed.

The amendments consist essentially in better defining the microemulsion composition by specifying the amounts and type of excipients used.
Furthermore independent novel claim 1 excludes the incorporation of any active pharmaceutical substance, whereas novel independent claim 2 does not contain this exclusion.

2) Claim 2 is related to a microemulsion suitable "for entrapping airborne particles". The applicant should bear in mind that if a known product is **in form** in which it is in fact **suitable for** the stated use, it would deprive the claim from novelty. Therefore as it seems that any microemulsion or **even emulsion disclosed in present cited prior art**, which is suitable or not for nasal or buccal administration, will be able to entrap airborne particles, these compositions anticipate though the intended use in claim 2 (see Guidelines CIII 4.8 and also CIV 7.6).

Put in other words it seems that claim 2 describes nothing more than a microemulsion composition.

If the applicant is able to show, e.g. by appropriate comparison tests, that differences do exist with respect to the features which will render the microemulsion specifically **adapted for** the intended use, it is questionable whether the independent claim 2 disclose all the features essential to entrap airborne particles (Art. 5 and 6 PCT).

The same remark applies to claim 14 with the intended use "to prevent airborne particles reaching exterior mucosa".

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3) Claims 13-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
Even if claim 14 does not specify the treatment of a pathological condition as such, the mere **prevention** of airborne particles from reaching exterior mucosal membranes of a mammal **encompasses** a therapeutical use, that is to say a **method of treating or preventing.**

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D13; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

5) Novelty and inventive step according to Art.33(2) and 33(3) PCT

5a) The subject-matter of claim 1 is novel because none of the cited prior art describes a microemulsion containing the excipients used in a range as described in claim 1, characterized in that it does **not** contain an active pharmaceutical substance.

5b) The subject-matter of claim 2 is nor novel nor inventive over D2 (or D3: p.88-89; D4: 472-473; D5). In particular D2 (see Table1; Example 3; claims 1-5, 9-10; p.3 L.26, p.6 L.5) describes a microemulsion containing:
a/ a non-polar lipid such as sesame oil, ethyl oleate;
b/ at least one polar solvent such water, PEG 400, ...;

c/ a surfactant such as polysorbate 80;
d/ a medium chain monoglyceride,
wherein a/, b/, c/ and d/ fall within the ranges described in present claim 2.
The microemulsion of D2 can be administered via nasal route (see p.3 L.26).
If the composition of D2 is capable to entrap both hydrophilic and lipophilic substances (see p.1 §1), it would be capable to entrap airborne particles (which has a hydrophilic core with a hydrophilic/electrostatic "envelop") (see also the remarks herein in §2).

D5 describes (see Table 1 on page 30;) a nanoemulsion containing:
a/ a non-polar lipid such as soybean oil (50-70%: see for example p.39 L.7)
b/ at least one polar solvent such as water, or glycerol or phosphate buffer saline (see claims 3,6 and 7) (15-30% see for example p.39 L.8)
c/ a surfactant such as polysorbate 60 or triton X-100 (octyl phenyl PEG)
d/ a polar amphiphilic lipid such as Generol (a polyethoxylated soya sterols) or glycerol monooleate (GMO see example 2 on p.64 and example 11 on page 83 L.8-12).
The amounts of the components are adapted to arrive at a nanoemulsion composition (see p.30 L.24-25) useful for decreasing infectivity of various pathogens (see for example p.3 L.27-28). The composition can be administered via nasal route (see p.49 L.21)

The above objections apply to claims 3-18, which do not appear to contain technical features that would establish novelty and/or inventive step for the subject-matter of claim 2.
Moreover it seems that the use and the benefits of some technical features are described and taught in D3-D13. Therefore dependent claims 3-18 are not novel and/or not inventive over D2 (or D3 or D4) taken alone or in combination with D3-D13.

5c) The subject-matter of claim 1 involves an inventive step for the following reason:

D1, which can be cited as the closest prior art, describes a o/w nasal emulsion for controlling the invasion of allergens which contains, according to the Example 3 of

the automatic traduction, 20 wt% of soybean oil, 0.2 wt% Tween 80, 0.5 wt% of hydroxylated lecithin, 1.0 wt% glycerol, 78.5 wt% water .

D1 distinguishes essentially from present application in that:
- the polar lipid is a hydroxylated lecithin present in a **very small amount, i.e. only ca. 0.5 wt%**, instead of a monoacyl glycerol as claimed in claim 1 which should be present in an amount between **20-40 wt%**,
- the amount of aqueous phase is much more higher than the amount of organic phase. According to the Examples in the automatic traduction of D1 the quantity of aqueous phase amounts 70 wt% in average. In present application it amounts up to 55 wt%. Put in other words, the microemulsion obtained in D1 is always a **O/W** (normal) emulsion, whereas in present application it would be rather a **W/O (reverse phase)**.

The problem to be solved consists in providing an alternative nasal microemulsion which is able to control the invasion of allergens.

D6 teaches that non-ionic surfactant nanoemulsion has a therapeutic potential for the prevention of influenza virus. However the composition is very different from the one of present application.

The microemulsion composition of **claim 1 is inventive** because none of the cited prior art will impel or suggest the skilled man in the art to formulate a composition containing the amounts and type of ingredients as described in claim 1, characterized in that it is efficient against allergens or virus by protecting the mucosa.
The protecting alleged effects were demonstrated in present application (see for example p.22 L.4-5, p.16 L.20-29, p.17 L.15-19, p.19 L.28-30).

In addition the O/W emulsion of D1 forms an oil film layer in the nasal cavity, whereas the rather W/O emulsion of present application does not "break" to produce an oil film upon application but remain as microemulsions. As a result of this, they retain the ability to quench the electrostatic charge present on the surface of airborne particles and also solvate the discharged particles by hydrophobic interaction (see p.6 in present application).

5d) Should the applicant renders the subject-matter of claim 2 novel by stressing out the importance a technical feature that is not described explicitly in prior art or by introducing into the claims the use of a **specific excipient or a specific range** or whatever, inventive step may be recognized **only if he demonstrates** that **a unexpected and improved effect** is attributed to the introduced technical feature that the skilled man in the art will not be able to deduct from the prior art.

As long as the applicant does not provide a **surprising and improved** effect of the combined features (which is not described in prior art), inventive step cannot be acknowledged because present application would be considered as an **obvious association** of features **resulting in an obvious accumulation** of known effects (see Guidelines CIV-Annex 2).

In particular, applicant's attention is drawn with the teaching of the following documents:

- D1 teaches the use of a nasal emulsion for controlling the invasion of allergens (see in particular example 3 of the automatic traduction: Soybean oil, Tween 80, hydroxylated lecithin, glycerol, water).
- D2 teaches, among the others, the benefit of using medium chain monoglyceride in a microemulsion.
- D3 and D4 teach the benefit of a microemulsion and how to prepare it.
- D5, among the others, describes for example the anti-virucidal effect of Tween 80 (see p.22 L.20-21) and a nanoemulsion containing the ingredients of claims 1-2.
- D6 and D12, among the others, teach that non-ionic surfactant nanoemulsion has therapeutic potential for the prevention of influenza virus.
- D7 (and D10) describes, among the others, the use of monoglyceride for intranasal route as amphiphilic agent.
- D8 teaches, among the others, the benefits of using tween 80 in a nasal composition.
- D9 teaches, among the others, the benefit of using sesame oil in a nasal composition.
- D11 describes, among the others, an emulsion containing budesonide, tocopherol, water, poloxamer and a polar lipid such as vitamin E TPGS (see example 18).
- D13 teaches, among the others, the use of a monoglyceride for its antimicrobial

effect.

Re Item VII

Certain defects in the international application

6) For the assessment of the present claims 13-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

7) Contrary to the requirements of Rule 5.1(a)(ii) PCT, it seems that the relevant background art disclosed in the documents D1,D2, D5-D6 and D12 is not mentioned in the description, nor are these documents identified therein.

For the regional phase:

8) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

9) In case if the applicant is on the opinion that he will provide convincing argumentations that will render the subject-matter of present application patentable, and if he finds it appropriate, he is requested to put the description in conformity with the present claims ("method of treatment"should be replaced by "second medical use " format), to delete the **superfluous** subject-matter which was not allowed with regard to novelty and inventive step.

10) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

11) The applicant is kindly requested to take account of the above **objections and give convincing argumentations.**

Claims

1. A microemulsion not containing any active pharmaceutical agent, said microemulsion comprising 5 to 35 wt% of a non-polar animal or vegetable oil, 10 to 55 wt% of at least one polar solvent selected from the group of water, a buffer, an alcohol, and mixtures thereof, and at lest one surfactant selected from a polysorbate, a poloxamer and a fatty acid polyoxyethylene, characterized in that it further comprises 20-50 wt% of a monoacyl glycerol.

2. A microemulsion suitable for entrapping airborne particles, characterised in that it consists of 5 to 35 wt% of a non-polar animal or vegetable oil, 10 to 55 wt% of at least one polar solvent selected from the group of water, a buffer, an alcohol, and mixtures thereof, and at lest one surfactant selected from a polysorbate, a poloxamer and a fatty acid polyoxyethylene, characterized in that it further comprises 20-50 wt% of a monoacyl glycerol.

3. The microemulsion as claimed in claim 1 or claim 2 wherein said mono-acyl glyceride is glyceryl monooleate, glyceryl monolinoleate or glyceryl monolinenoleate.

4. The microemulsion as claimed in any of claims 1 to 3, wherein said non-polar animal or vegetable oil comprises said sesame oil.

5. The microemulsion as claimed in any of claims 1 to 4, wherein at least one component of said polar solvent has a pH exceeding pH 5.5.

6. The microemulsion as claimed in any of claims 1 to 10, wherein said polar solvent comprises propylene glycol and/or polyethylene glycol and/or saline solution.

7. The microemulsion as claimed in any of claims 1 to 6, wherein said surfactant has a hydrophilic-hydrophobic balance exceeding 7.

8. The microemulsion as claimed in any of cliams 1 to 7 wherein said polysorbate is polysorbate 80.

9. A composition suitable for administration to peripheral membrane linings of the nose, the eyes, the ears, the pharynx, and/or the larynx of a mammal, characterized in that it comprises a pharmaceutically effective amount of a microemulsion as claimed in any of claims 1 to 8.

10. A mouth or nasal spray device containing the microemialsion as claimed in any of claims 1 to 8.

11. A filter device comprising the microemulsion as claimed in any of claims 1 to 8.

12. A mouth or nasal spray device containing the composition as claimed in claim 9.

13. A method for preventing allergic rhinitis in a subject, caused directly or indirectly by airborne particles, said method comprising contacting at least one surface of said subject with a composition as claimed in claim 8.

14. A method of preventing airborne particles reaching exterior mucosal membranes of a mammal, said method comprising the step of administering to said exterior mucosal membranes of said mammal a prophylactically effective amount of a composition as claimed claim 9.

15. The method as claimed in claim 14, wherein said composition is administered buccally or intranasally.

16. A microemulsion as claimed in any of claims 1 to 8 for use in therapy.

17. The use of a micro-emulsion as claimed in any of claims 1 to 8 in the manufacture of a medicament for the treatment or prevention of a disease caused directly or indirectly by airborne pollen.

18. The use as claimed in claim 17 wherein said disease is allergic rhinitis.